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Role of C–C chemokines in Takayasu's arteritis disease

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Abstract

Background: Takayasu's arteritis (TA) is a chronic obliterative inflammatory disease. Inflammatory cell infiltration and destruction of the vessel wall in TA strongly suggest that cell mediated immunological mechanisms play an important role in the pathogenesis of this disease. Therefore, in the present study our aim was to focus on the role of chemokines and adhesion molecules in patients with Takayasu's disease.
Methods: Twenty-one patients with clinically defined TA and 21 healthy control volunteers were recruited by using the standard criteria. Patients with TA were divided into those with clear-cut clinically active or inactive disease based on vasculitis activity score.
Results: MCP-1 and hRANTES were significantly increased in patients with TA as compared to controls. MCP-1 and hRANTES values were reliably able to distinguish between patients with active disease vs. subjects in remission. sVCAM-1 levels remained unaltered between patients and controls.
Conclusions: C–C chemokines can be used as reliable markers/diagnostic tools in determining the activity of Takayasu's arteritis.

Keywords: Takayasu's arteritis; C–C chemokines; Adhesion molecules; Inflammation; Cytokines

1. Introduction

A preponderance of evidences from clinical and experimental studies supports the notion that inflammation plays an important role in a wide range of vascular disease and has focused attention on the signals that initiate cellular infiltration of vascular diseases. Takayasu's arteritis (TA) is a chronic obliterative inflammatory disease, involving large elastic arteries, aorta and its main branches [1]. The female and male ratio shows significant variation among different ethnic groups being 24:1 among Japanese and 6:1 in Korean patients [2], 2.1:1 in India [3], 1.2:1 in Israel, 2.15:1 in Thai patients [4], 3.6:1 among the Turkish patients [5] and 6.9:1 in Mexican [6]. The pathogenesis of this morbid condition is still unknown. Epidemiologically it is found mostly in females of reproductive age and is more prevalent in Asian and Latin American countries [7,8].

Adventitial inflammation is the defining feature in many forms of arteritis. Inflammatory cells in the adventitia may likely produce many active chemokines and members of RANTES (regulated on activation, normal T-cell expressed and secreted) gene family, which may increase the inflammatory state of the tissue. Comparable to the observations in atherosclerosis, about the role of cytokines, chemokines as well as adhesion molecules like vascular cell adhesion molecule-1 (VCAM-1) in the intima and adventitia of atherosclerotic vessel suggest that these observations may also be important in the setting of arteritis.

In vitro data indicates that cytokines such as interleukin-1, tumor necrosis factor-α (TNF-α) and interferon-γ induce cell surface expression of VCAM-1 or intercellular adhesion molecule-1 (ICAM-1) in endothelial cells and smooth muscle cells [9,10]. In addition, induction or up regulation of cell surface VCAM-1, or ICAM-1 has been observed in a variety of inflammatory diseases [11].

Once the inflammatory response has begun in the adventitia, cytokines released by inflammatory cells present in the adventitia may contribute to the maintenance of

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chemokines and adhesion molecule expression, thus further stimulating the inflammatory response. C–C family of chemokines, e.g. MCP-1 (monocyte chemotactic protein-1) and RANTES have been shown to be involved in trafficking of blood borne monocytes to the site of inflammation and are implicated in the pathogenesis of several inflammatory diseases [12].

Noris et al. [13] have reported a close correlation of RANTES levels in Italian subjects with disease activity. Noguchi et al. [14] have found significant high levels of sVCAM-1 in TA subjects as compared to the healthy controls in Japanese populations and hypothesized that increased levels of sVCAM-1 may have some relation with disease activity. We are here reporting the status of monocyte chemotactic protein-1 (MCP-1) levels in Takayasu's disease. To the best of our knowledge MCP-1 levels have not been reported in patients suffering from TA in any ethnic populations.

Therefore, keeping in view the inflammatory aspects of the disease and significant variations in different ethnic groups, in the present study we have focused on the role of the chemokines like RANTES and MCP-1 and adhesion molecule VCAM-1 in the subjects with Takayasu's arteritis in North Indian population. These molecules may play a significant role during the inflammatory process in TA and thus, unveil some more hidden facts of the disease.

2. Materials and methods

2.1. Clinical profile of study subjects

Twenty-one patients with TA were enrolled at a special clinic in Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh. A modified diagnostic criterion of Sharma et al. [15] was used to clinically diagnose these 21 patients of TA with a sensitivity of 92.5% and a specificity of 95%. The criteria consisted of five modifications of Ishikawa's criteria [16]. These included (a) removal of the obligatory criteria of age less than 40 years, (b) inclusion of characteristic signs and symptoms as major criteria, (c) removal of age in defining hypertension, (d) deletion of absence of aorta-iliac lesion in defining abdominal aortic lesion, and (e) an addition of coronary artery lesion in absence of risk factors. A detailed clinical examination with special emphasis on asymmetry or absence of arterial pulsation, presence of a bruit over the aorta or its branches, blood pressure recording in all four limbs and an ophthalmic examination were done in all the patients. The blood pressure measurement was carried out as per JNC VI recommendations [17].

Active disease was arbitrarily defined in accordance with National Institute of Health (NIH) as new onset or worsening of at least two of the following four features: (i) signs and symptoms of vascular inflammation or ischemia (claudication, decreased or absent pulses or blood pressure in extremities, bruits or carotidynia); (ii) elevated ESR; (iii) angiographic abnormalities; and (iv) systemic symptoms not attributable to another disease, e.g. fever, polyarthralagia, polymyalgias.

A complete angiogram was done for each and every TA subject who were suspected to be in active phase of disease. In other subjects, the absence of new vascular lesions was confirmed by either angiography or ultrasonography. Finally, the scoring for subjects was done according to the above-mentioned NIH criteria. Subjects, which were found to have new onset or worsening of each of the above-mentioned feature, were scored 1; a score of 2, 3 or 4 defined active disease.

In the present study, 16 (76.2%) subjects were in active phase when they were enrolled in the study, and 5 (23.8%) were in remission.

Management of the TA subjects was based mainly on the symptomatology and immune basis of disease. Immunosuppressive therapy was the mainstay of the medical therapy during the active stage of disease. The steroids like prednisolone, wysolone were the drug of choice in these study subjects.

2.2. Experimental design and protocol

Biochemical laboratory investigations included a complete hemogram, urine analysis, blood biochemistry and fasting blood glucose examination. The study was approved by The Medical Ethics Committee of Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh.

2.3. Control subjects

Twenty-one normal, healthy, unrelated subjects of both sexes, belonging to same ethnic origin and socio-economic background were included in the present study as controls. The following exclusion criteria was used, e.g. absence of a clinical history of cardiovascular disease, collagen disease, autoimmune disease and any current inflammatory disorder.

All patients and controls represented the ethnic group of North Indian subjects from the states of Punjab, Haryana, Himachal Pradesh, Uttar Pradesh and Delhi. Informed consent was taken from all the patients and control subjects prior to their participation in the study.

2.4. Sampling

Venous blood was collected from the overnight fasted individuals in the morning from antecubital vein into plain sterile tube for serum and in EDTA for plasma. Serum/plasma was separated and stored at −80 °C for further analysis of chemokines and adhesion molecules.

Table 1
Physical characteristics of the study subjects ($n=42$)

Investigations	TA ($n=21$)	Controls ($n=21$)
Age (years)	26±12	28±10
Sex ratio (M:F)	5:16	7:14
Blood pressure		
Systolic (mm Hg)	143±28*	122±2
Diastolic (mm Hg)	88±22*	80±4
BMI (kg/m^2)	27±6**	23±3
Smokers***	2	3
Alcohol use***	2	3

n=Number of subjects.
Data are Mean±S.D.
* $p<0.01$ vs. control.
** $p<0.05$ vs. control.
*** Occasionally.

2.5. Determination of monocyte chemotactic protein-1 (MCP-1)

Circulating serum levels of monocyte chemotactic protein-1 (MCP-1) were determined in 21 patients with TA and 21 control subjects by using commercially available ELISA kit obtained from Amersham Biosciences (RPN 2769). The minimum detectable concentration in the assay was 51 pg/ml with an intra-assay variability of 10% and an inter-assay variability of 10%.

2.6. Determination of human regulated on activation, normal T-cell expressed and secreted (hRANTES)

Serum levels of hRANTES were determined in 21 TA patients and equal number of control subjects by using commercially available ELISA kit obtained from Amersham Biosciences (RPN 2771). The minimum detectable concentration in the assay was 51.2 pg/ml with an intra-assay variability of 10% and an inter-assay variability of 10%.

2.7. Determination of soluble vascular cell adhesion molecule-1 (sVCAM-1)

Soluble vascular cell adhesion molecule-1 (sVCAM-1) was determined in the serum of 21 TA patients and their controls by using commercially available ELISA kit obtained from R&D systems, USA (BBE3). The minimum detectable concentration in the assay was 20 ng/ml with an intra-assay variability of 5% and an inter-assay variability of 10%.

3. Results

3.1. Physical characteristics

The clinical characteristics of the TA patients and controls are shown in Table 1. Total number of the TA patients and control subjects were twenty-one each. The male/female ratio in TA patient group was 5:16 as compared to 7:14 in the control subjects. The age range of TA patients was 17–53 years, where as in controls it was 15–49 years. As far as clinical parameters are concerned, the commonest mode of presentation was hypertension. Other common features included asymmetry of pulses, vascular bruits and breathlessness [18]. We observed a higher blood pressure, both systolic and diastolic in TA patients as compared to their control counterparts, the value being statistically significant ($p<0.05$). The body mass index (BMI) was also moderately higher in subjects with TA as compared to their control counterparts ($p>0.05$; Table 1).

3.2. Biochemical profile

All the study subjects underwent baseline biochemical and hematological investigations. Erythrocyte sedimentation rate (ESR) and total leukocyte count (TLC) values were higher in patients with active disease than in patients in remission as well as in their control counterparts ($p<0.05$), which suggests an underlying inflammation. We observed no statistically significant difference between patients and control subjects as far as blood urea, serum creatinine and uric acid levels are concerned ($p>0.05$; Table 2). In these patients an expansion of $CD4^+$ subset, increase in $CD4^+/CD8^+$ ratio was also noted (data not shown). These features suggest that circulating lymphocytes in these TA patients were in the activated state. Further, we noted the presence of dendritic cells, which may contribute to the inflammatory process by in situ activation of T lymphocytes.

3.3. Circulating levels of monocytic chemotactic protein-1 (MCP-1)

The serum levels of MCP-1 were determined in TA patients and control subjects. The circulating levels of MCP-1 were significantly higher in serum of patients with Takayasu's arteritis (402.9±235.3 pg/ml) as compared with normal healthy subjects (304.8±74.3 pg/ml). Further, we also observed remarkably higher levels of MCP-1 in TA patients with active disease (476.3±222.4 pg/ml) as compared to the TA patients who were studied during remission of the disease (168±30.3 pg/ml). Also, the

Table 2
Biochemical Investigations in TA patients

Investigations	TA ($n=21$)	Controls ($n=21$)
ESR (mm)	23.91±16.81*	15.41±10.98
Hb (g/dl)	10.71±1.41*	14.8±1.89
TLC (mm^3)	8867.66±2796.18	9008.45±2489.35
Urea (mg/dl)	28.2±8.8	27.4±7.9
Creatinine (mg/dl)	0.84±0.3	0.83±.04

n=Number of subjects.
Data are Mean±S.D.
ESR—erythrocyte sedimentation rate, Hb—hemoglobin, TLC—total leukocyte count.
* $p<0.05$ vs controls.

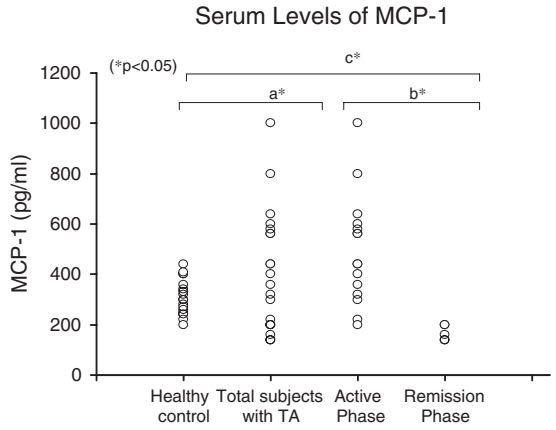

Fig. 1. Circulating MCP-1 levels in patients with Takayasu's arteritis ($n=21$), healthy controls ($n=21$) and in TA subjects studied during active phase ($n=16$) and in remission ($n=5$). (a) Total TA subjects vs. controls (402.9±235.3 pg/ml vs. 304.8±74.3 pg/ml). (b) TA subjects in active phase vs. remission (476.3±222.4 pg/ml vs. 168±30.3 pg/ml). (c) Controls vs. TA subjects in remission (304.8±74.3 pg/ml vs. 168.0±30.3 pg/ml).

difference between patients with active TA disease and those in remission was statistically significant ($p<0.05$). Circulating levels of MCP-1 in each study subject are shown (Fig. 1).

3.4. Levels of soluble vascular cell adhesion molecule-1 (sVCAM-1)

In contrast to the observations with MCP-1, we observed higher sVCAM-1 levels in serum of normal healthy controls as compared with the patients of TA (516.5±129.2 ng/ml vs. 444.2±225.3 ng/ml). When the sVCAM-1 values were compared between patients with active disease and with

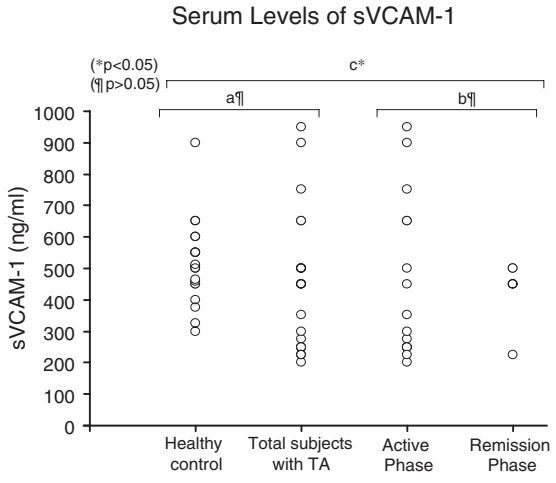

Fig. 2. Circulating sVCAM-1 levels in patients with Takayasu's arteritis ($n=21$), healthy controls ($n=21$) and in TA subjects studied during active phase ($n=n=16$) and in remission ($n=5$). (a) Total TA subjects vs. controls (444.2±225.3 ng/ml vs. 516.5±129.2 ng/ml). (b) TA subjects in active phase vs. remission (450.2±253.1 ng/ml vs. 425±114.6 ng/ml). (c) Controls subjects vs. TA subjects in remission (516.5±129.2 ng/ml vs. 425.0±114.6 ng/ml).

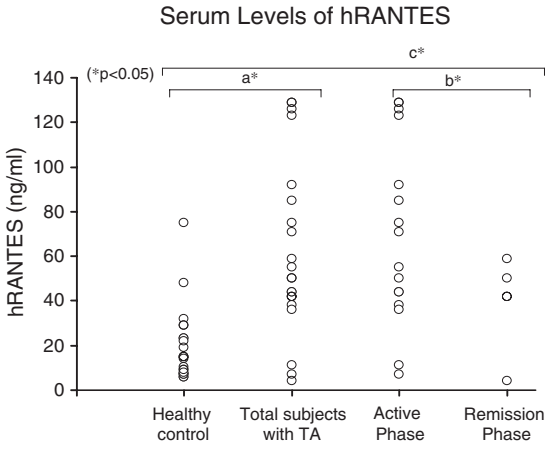

Fig. 3. Circulating hRANTES levels in patients with Takayasu's arteritis ($n=21$), healthy controls ($n=21$) and in TA subjects studied during active phase ($n=16$) and in remission ($n=5$). (a) Total TA subjects vs. controls (62.5±39.1 ng/ml vs. 19.7±16.7 ng/ml). (b) TA subjects in active phase vs. remission (69.7±41.0 ng/ml vs. 39.4±21 ng/ml). (c) Controls subjects vs. TA subjects in remission (19.7±16.7 ng/ml vs. 39.4±21 ng/ml).

those in remission, slightly lower levels were observed in subjects with remission of the disease. However, these levels remained still lower than control subjects and were statistically nonsignificant. sVCAM-1 levels in each control subject ($n=21$) and each TA patient [active ($n=16$), remission ($n=5$)] are shown in Fig. 2.

3.5. Levels of human regulated on activation, normal T-cell expressed and secreted (hRANTES)

The serum levels of hRANTES were observed to be significantly higher in patients with Takayasu's arteritis (62.5±39.1 ng/ml) as compared to the normal healthy control subjects (19.7±16.7 ng/ml). We also observed significantly higher levels of hRANTES in TA patients with active disease as compared to subjects with TA studied in remission (69.7±41.0 vs. 39.4±20.1 ng/ml), however, the difference remained statistically significant ($p<0.05$). Individual levels of hRANTES in TA patients and their control counterparts are plotted in Fig. 3.

4. Discussion

TA is a chronic non-specific inflammation of unknown etiology and its pathogenesis is far from clarified. In spite of current treatments, progression of vascular lesion is observed frequently and the disease still remains a therapeutic challenge.

TA is characterized histologically as a "panarteritis", involving all the layers of the arterial wall. The inflammatory process observed in the early stage of the disease consists of infiltration of lymphocytes and monocytes predominantly in the adventitia, also involving the outer third of the media. The advance phase of the disease is

characterized by the medial and adventitial fibrosis and variable degree of intimal thickening resulting in luminal narrowing and sometimes aneurysmal dilation due to medial destruction. Affected areas consist of a mixture of both active, productive inflammatory lesions and old fibrotic lesions [19,20]. At this stage positive production of inflammatory cytokines and/or adhesion molecules around these areas is remarkable, suggesting a chemotactic activity of T-cells and monocytes [14].

The most commonly used NIH (National Institute of Health) criteria for active disease have been accepted as reliable measure of disease activity but require an angiographic examination for scoring [18]. The invasiveness and cumulative radiation toxicity of this procedure limits its use in monitoring disease progression. ESR and C-reactive protein (CRP) have been used as conventional inflammatory markers; however, they lack sensitivity and specificity [21,22]. Kerr et al. observed that 72% patients with active TA had elevated ESR. Our observations are in accordance with the observation of Kerr et al. [23], as all TA patients with active disease showed elevated ESR and CRP levels. In these patients, an expansion of $CD4^+$ subset, increase in $CD4^+/CD8^+$ ratio was also noted (data not shown). These features suggest that circulating lymphocytes in these TA patients were in the activated state. Further, we noted the presence of dendritic cells, which may contribute to the inflammatory process by in situ activation of T lymphocytes.

Various studies in the literature have demonstrated that immune inflammation is a typical feature of TA and that the interaction between dendritic cells and lymphocytes may be important in the control of immune reactions in this vascular pathology [24,25].

The recruitment of monocytes from peripheral vasculature to an area of chronic inflammation is a complex phenomenon. This complex process is likely mediated to a large extent by chemotactic cytokines that are expressed via a cytokine cascade. A number of diseases that are difficult to manage are characterized by significant infiltrates of monocytes [26]. Lymphocytes from TA patients are shown to be sensitized against arterial antigen and are capable of enhancing vascular damage via large vessel antigen induced by activation and cytokine release. This statement is further strengthened by the fact that inflammatory cell infiltrates in aortic tissue samples from patients with TA consist mainly of γδT lymphocytes, NK cells, macrophages, and CTL and T-helper cells [13].

What is the signal that drives the mononuclear leukocytes to infiltrate large vessels in these TA patients? We have tried to address this question by measuring the circulating levels of the chemokines and adhesion molecules like MCP-1, RANTES and sVCAM-1 in patients with Takayasu's disease.

RANTES and MCP-1 belong to a family of potent chemotactic cytokines that regulate the trafficking and are rapidly unregulated at the site of vascular inflammation. They play a pivotal role in immune system development and deployment [27,29,30]. The extent to which chemokines such as MCP-1 and RANTES contribute to the retention and activation of macrophages in advanced lesions is unclear.

In this study of 21 patients with TA, we found that all patients with TA had increased serum concentration of MCP-1 and RANTES as compared with normal healthy subjects. Further, both MCP-1 and RANTES levels were remarkably able to discriminate between the patients with active TA disease with those study subjects who were in remission. As far as the literature is concerned, ours is the first study to report MCP-1 levels in patients with Takayasu's arteritis patients.

IL-6, IL-1 and RANTES have been shown to be released in large amounts by infiltrating inflammatory cells within damaged tissues as well as by circulating inflammatory cells and very likely help to maintain the aberrant immune activation by promoting endothelial cell activation and by inducing lymphocyte infiltration, thereby, increasing expression of adhesion molecules and facilitation of leukocyte traffic [31].

Both MCP-1 and RANTES molecules have been shown to have a compensatory role in balancing the impaired mechanism involved in immune response during ageing [32] and inflammation [28]. Few studies have shown that MCP-1 expression is increased in atherosclerotic lesion and injured arteries [27,31]. It has also been implicated as a key player in recruitment of monocytes from blood into early atherosclerotic lesions, the development of intimal hyperplasia after angioplasty as well as in vasculogenesis and in aspects of thrombosis [28]. Besides promoting the transmigration of circuiting monocyte, MCP-1 exerts various effects on monocytes including cytokine production and adhesion molecule expression [33].

Both these chemokines might reflect different status of activation and/or responsiveness of monocytes and lymphocytes from TA patients, thereby, contributing to the impairment of immune system in these patients. In this regard, our findings are in accordance with the finding of Noris et al. [13] who reported that monitoring the levels of RANTES and IL-6 in serum might enable the clinician to adopt better therapeutic measures for patients on an individual basis.

We observed lower MCP-1 levels in subjects of TA in remission, much lower than even healthy controls. This pattern reflected on RANTES levels also. This finding is intriguing. It has been reported in the literature that corticosteroids as well as immunosuppressive agents added to corticosteroids can bring TA into remission in many patients. Dexamethasone, in a dose dependent manner, has been shown to inhibit the expression of IL-8 and MCP-1 in corneal fibroblasts induced by proinflammatory cytokines both at mRNA and protein levels [34]. It is possible that when the subjects with active TA disease were brought into remission, could have reflected the effects of steroid therapy during maintenance levels in these patients.

Regarding inflammation, cell adhesion molecules (CAM) mediate rolling and transendothelial migration of circulation leukocytes into the vessel wall [35,36]. The cellular origin of CAMs is uncertain, but possible cellular sources in vascular structure include endothelial cells, smooth muscle cells (SMC) and leukocytes. In the present study, we have studied soluble vascular cell adhesion molecule (sVCAM-1) in patients with TA and their control counterparts. As cell adhesion molecules along with cytokines play a pivotal role in the accumulation of inflammatory cells at the endothelium and are known to regulate their interaction with the vessel wall, these molecules are of particular interest [37]. The expression of vascular cell adhesion molecule-1 (VCAM-1) and intracellular cell adhesion molecule-1 (ICAM-1) has been shown to be unregulated on endothelial cells in the lesions, and the levels of plasma soluble forms of these molecules have been correlated with the surface expression of CAMs [35,36,38]. Elevated levels of CAM have also been reported in patients with CAD as compared to in the normal healthy controls [39,40].

However, in contrast to the above observations we observed no significant difference between the TA patients and normal healthy subjects as far as sVCAM-1 levels are concerned. Further, sVCAM-1 levels were also unable to distinguish between subjects with active TA disease and in those patients who were in remission. This finding is intriguing. Although, the cellular sources of sVCAM-1 in TA are still under investigation, recent work has demonstrated chemokines expression following cell-to-cell and cell-to-matrix adhesion. These findings demonstrate that adhesion and not a soluble stimulus in some cases is responsible for initiating or augmenting chemokines expression. Smith et al. [41] hypothesized that effects of adhesion are not limited to leukocytes and both immune and non-immune cell types act as potential sources of adhesion mediated chemokine expression. As a recruited leukocyte encounters different adhesion substrates such as endothelial cells, basal membrane, extracellular matrix and fibroblasts, the expression of chemokines from both the leukocytes and substrate may be initiated, inhibited or augmented.

Another, possibility of not gaining clear-cut evidence could be the small number of patients included in this study and the stringent inclusion criteria for inclusion of these patients in the study. Our findings are contrary to the findings of Noguchi et al. [14] who reported increased levels of sVCAM-1 in patients with TA as compared to the controls whereas sICAM-1 levels were not altered. They suggested that measurement of sVCAM-1 may have potential as a non-invasive tool for diagnosis of this disease activity.

Same workers also reported that when the levels of sVCAM-1 and sICAM-1 were compared between TA patients and control subjects based on their age, significantly higher levels of sVCAM-1 were found in individuals who were 50 years old compared to those <39 years old. In our study, however, we had only one patient with TA with age over 50 years. Further, we did not observe any significant correlation of sVCAM levels and MCP-1 levels with age. However, hRANTES levels correlated positively with age in this study.

Our study reports are in agreement with the findings of Hoffman et al. [24] who determined multiple surrogate markers of disease activity including sVCAM-1 in patients with TA. They reported that no marker was reliably able to distinguish between age-matched healthy volunteers and patients with active TA.

Biological expression of these important vascular chemokines has been shown to be further mediated by NF-kappa B [42]. It is anticipated that more precise delineation of these patterns of gene expression will help to identify molecular targets for prevention and treatment of TA.

So far our knowledge and survey of the literature shows that this is a first report on MCP-1 expression in patients with TA. Future work related to the study of regulation of chemokine expression will provide insight into the pathogenesis of many human diseases where chemokines have a central role. Further, our data strongly demonstrates that chemokines such as RANTES and MCP-1 mediate inflammatory response and, thus can be studied as potential diagnostic tools and markers of disease activity. Therefore, inhibition of chemokines or chemokines receptors might be novel therapeutic targets to combat this disease.

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